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Primary Leptomeningeal Histiocytic Lymphoma in a Young Child

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A 20-month-old boy had an 8-week history of vomiting, lethargy, generalized muscle weakness, and seizures. There was no history or clinical signs of an underlying systemic disease or an immunodeficiency. Cerebrospinal fluid (CSF) had 99 nucleated cells/cu mm, malignant cells, high protein and normal glucose. CT and MRI scans showed diffuse meningeal enhancement around the brain and spinal cord, but no parenchymal involvement. Biopsy of the leptomeninges showed malignant cells with marked nuclear pleomorphism and prominent clear to eosinophilic cytoplasm. The immunohistochemical studies were positive for histiocyte-macrophage markers and were negative with T and B cells, Ki-1, neural and glial cell antibodies. Multiple tests revealed no other site of disease. The patient died 3 months after onset of treatment despite intensive IV and intrathecal chemotherapy. We have not found any other reported case of primary histiocytic leptomeningeal lymphoma in a young child.

Key words: children, primary leptomeningeal lymphoma, histiocytic lymphoma

INTRODUCTION

Primary central nervous system lymphomas (PCNSL) account for 7% of all lymphomas affecting the central nervous system (CNS) [1, 2]. They usually involve the brain parenchyma as focal or multifocal tumors [2, 3]. Meningeal invasion occurs in 3.8% to 8.5% of all lymphomas and is commonly associated with widespread progression [1–3]. Primary leptomeningeal lymphomas (PLML) are exceedingly rare, particularly in children and in patients with no underlying immunodeficiency. Although there are few reports of PLML in children, to our knowledge there are no reports of primary leptomeningeal histiocytic lymphoma. We present a young child with extensive infiltration of histiocytic lymphoma in the meninges around the brain and spinal cord, but with no evidence of parenchyma involvement of the neuraxis or dissemination to other organs.

CASE HISTORY

A 20-month-boy had a 2-month history of recurrent vomiting, irritability, fatigue, muscle weakness and weight loss. He became increasingly somnolent and had difficulty focusing and following. On the day of his admission to the hospital he had a seizure. On admission his vital signs were normal and he was afebrile. Although lethargic, he responded to touch and voice. His pupils were dilated and sluggishly responsive to light. He had bilateral horizontal nystagmus, papilledema, mild generalized muscle weakness, bilateral facial weakness, bilateral Babinski signs and normal reflexes. There was no meningismus, lymphadenopathy, hepatomegaly or skin lesions. There was no history of fever, diarrhea, chronic cough, bleeding diathesis, head trauma or exposure to toxins. His development had been normal except for mild speech delay. His mother was HIV-negative.

The EEG on admission was diffusely slow, with epileptiform discharges in both hemispheres, most notably in the parasagittal regions. There was an independent seizure focus in the left temporal region. Follow-up EEGs showed delta rhythms predominantly in the left temporal regions. The initial CT and MRI scans of the brain and spinal cord revealed marked leptomeningeal enhancement, most prominent in the basal cisterns and tentorium cerebelli. The ventricles were dilated and the entire spinal cord was covered with thick nodular enhancing tissue. The brain and spinal cord parenchyma was normal (Fig. 1). The opening pressure of the initial lumbar puncture was 36 cm of water. There were 17 red blood cells/cu mm and 51 mononuclear cells/cu mm, 22% were lymphocytes and 78% monocytes. No malignant cells were found. The total protein was 245 mg/dL and glucose 72 mg/dL.

A second lumbar puncture obtained 3 days later revealed an opening pressure of 7 cm of water; there were 99 nucleated cells with 25% segmented neutrophils, 10% histiocytes and the rest were mononuclear cells. There were clumps of malignant-appearing cells of unknown type. The total protein was 270 mg/dL and glucose 50 mg/dL. The Gram stain, Acid-fast bacilli (AFB) stain and

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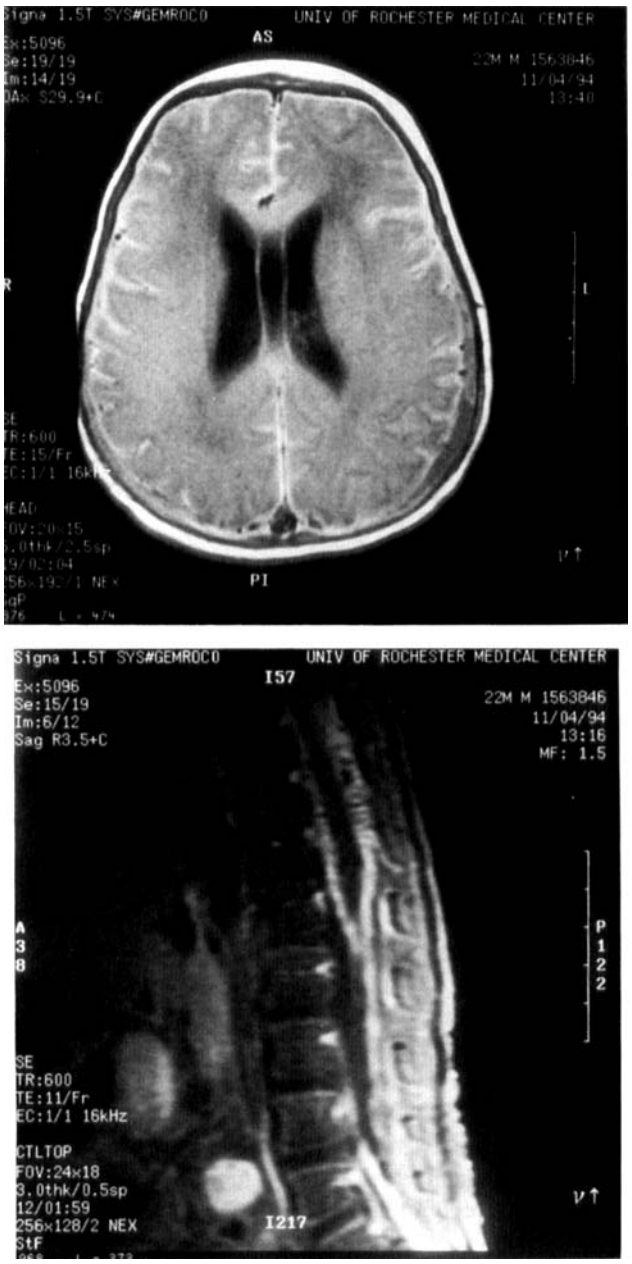

Fig. 1. MRI of the brain and spinal cord after infusion of gadolinium. T1-weighted images show prominent diffuse, thick leptomeningeal enhancement. There are no parenchymal or ependymal enhancing lesions in the brain and spinal cord. The ventricles are dilated.

cryptococcal antigen were negative. Multiple cultures of the cerebrospinal fluid for bacteria, virus, and fungi were all negative. Cysticercus antibody was negative. The HIV test was negative. The serum ferritin was normal. The bone marrow biopsy, bone scan, chest x-ray and abdominal CT scan were all normal. The tuberculin skin test was negative and the erythrosedimentation rate (ESR) was normal.

A meningeal biopsy (Fig. 2) showed obliteration of the subarachnoid space by neoplastic cells. Most of the

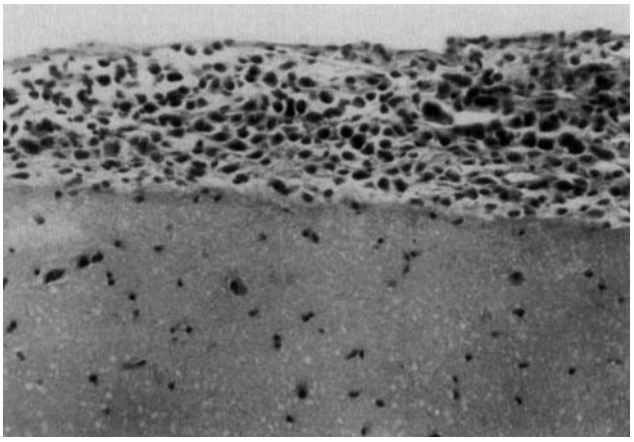

Fig. 2. The subarachnoid space is filled with neoplastic cells (H-E stain).

cells were of medium to large size and had marked nuclear pleomorphism. The nucleoli were large and the cytoplasm was prominent and clear to eosinophilic. Immunoperoxidase stains were focally positive for common leukocyte antibody (CLA), for histiocyte-macrophage markers (HAM-56, CD 68, alpha-1 antichymotrypsin [ACT], alpha 1 antitrypsin [AT], LN2 lysozyme, and nonspecific esterase). They were most effectively labelled with antibodies to ACT and AT, as well as for vimentin. The cells were negative for the glial cell markers (GFAP and S-100), neural markers (chromogranin, synaptophysin, PGP 9.5 and neuron-specific enolase), muscle markers (desmin 33 and muscle specific actin), epithelial membrane antigen, cytokeratins (CAM 5.2 and KER AE), T and B cell markers, and Ki-1 (CD-30). The morphololgy and immunohistochemical stains were most consistent with a histiocytic lymphoma.

In Emergency Department, the patient was treated with IV lorazepam and diphenylhydantoin. Carbamazepine and phenobarbital were later added to improve seizure control. Chemotherapy included 3 cycles of IV cyclophosphamide, idarubicin, vincristine and dexamethasone. He also received intrathecal methotrexate and cytosine arabinoside. A follow-up MRI scan after the second cycle showed essentially no change in the extent of diffuse meningeal enhancement, and no parenchymal involvement. Several head CT scans with contrast during his hospitalization also showed no signs of parenchymal dissemination. Repeat lumbar puncture after the third chemotherapy cycle revealed no malignant or reactive cells.

Initially, the patient was able to make noises, to focus, and he spoke few words. He could hold his bottle and drink. Later in the course of illness, the periods of alertness and spontaneous motor activity steadily declined. Seizures occurred almost daily; most of them had focal onset. A permanent ventriculo-peritoneal (VP) shunt was

placed because of persistent ventricular dilation. He continued to deteriorate; he developed progressive muscle weakness, most marked in the lower limbs. His lower limbs eventually became completely paralyzed and flaccid, with no motor response even to painful stimulus. He developed bilateral ophthalmoparesis, lost the ability to suck, had marked difficulty with swallowing and became areflexic. He continued to show no evidence of systemic involvement with the lymphoma. Fourteen weeks after his admission he had respiratory arrest and died. Consent for autopsy was denied.

DISCUSSION

Although an autopsy was not performed in the present case, he showed no signs of dissemination outside the CNS, as evidenced by the normal CT scan of the chest and abdomen, normal bone scan and bone marrow and the lack of adenopathy on physical examinations. He also had no evidence of gross spinal cord or brain parenchyma involvement as demonstrated by multiple head CT scans and MRIs of the brain and spinal cord. The patient had normal growth and development, was not lymphopenic, had negative HIV test and had no evidence of an immunodeficiency, which might have predisposed him to lymphoma.

The immunohistochemistry studies performed on the leptomeningeal infiltrate were positive for histiocyte-associated antigens and negative for antigens commonly present in type T or B cells lineage, particularly the Ki-1 (CD-30) lymphoma. These findings were most consistent with an histiocytic lymphoma.

The existence of PLML without extrameningeal involvement is extremely rare and because infiltration of the cranial and or spinal leptomeninges can occur in any type of systemic non-Hodgkin's lymphoma (NHL), the differentiation of PLML from secondary leptomeningeal invasion can be difficult to discern at the onset. A thorough evaluation to exclude other sites of CNS involvement as well as the more common sites outside of the CNS is mandatory. Griffin et al. [4] reported 21 cases (ages 2–61 years) of lymphomatous meningitis; all had disseminated disease. In 15 cases the diagnosis of histiocytic lymphoma was made but no immunologic studies were performed to accurately classify the lymphomas. The other cases were classified as poorly differentiated lymphocytic lymphoma, undifferentiated lymphoma and Hodgkin's disease. Other series of PCNSL include predominantly primary lymphomas with only a handful of reports citing isolated leptomeningeal disease. Grove and Vyberg [2] cited three seperate studies with a total of 47 cases of PCNSL, which were examined with a panel of monoclonal antibodies. Most of them were B-cell neoplasms; none were T-cell lymphoma. He also found 13 previously reported cases of well-documented T-cell PCNSL. In 5 of them, the lymphoma was apparently confined to the leptomeninges. The median age of these patients was 45.5 years (range 17–67 years); none of them had clinical signs of immunodeficiency and HIV testing performed in four cases was negative. Lachance et al. [5] reported nine patients (ages 35–70 years) with NHL presented with leptomeningeal involvement. Of five patients in whom immunohistochemistry data were available, four had B-cell lymphoma and one had a diffuse mixed cell tumor of T-cell type. Six of the nine patients died 2 weeks to 24 mos after onset of therapy; three were alive at 11, 15 and 29 months after diagnosis.

The poor response to intensive chemotherapy in this case is consistent with previous reports [5–7]. The overall prognosis for survival in all forms of lymphomatous neurologic disease has been considered poor, despite aggressive therapy with systemic chemotherapy, neuraxis irradiation, intrathecal chemotherapy, or some combination of all three [5–7]. Chemotherapy directed to the subarachnoid space, via Ommaya reservoir or intrathecally, has been advocated as the treatment of choice to achieve complete remission, freedom or recurrences and to prolong survival in PCNSL with meningeal involvement [8].

It is not known whether responses to treatment and survival are different for PLML patients than for other PCNSL. Meaningful correlations between histology, treatment, and survival of patients with PLML have not been possible because of the limited number of cases reported to date, the histologic heterogeneity, and varying degrees of dissemination.

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